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October 18, 2005

Division of Dockets Management
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061 (HFA-305)
Rockville, Maryland 20852

Re: Docket No. 2005P-0383
Comments to Citizen Petition Filed on
Behalf of Savient Pharmaceuticals, Inc.

Dear Sir or Madam:

Please accept this correction to our previous comments dated, October 17, 2005 to Docket No. 2005P-0383. This substitution corrects a spelling error in the original comment.

Sincerely,

Josephine M. Torrente

2005P-0383

CR 1

JMT/dh

Enclosure

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Re: Docket No. 2005P-0383
Comments to Citizen Petition Filed on
Behalf of Savient Pharmaceuticals, Inc.

Dear Sir or Madam:

These comments to the September 19, 2005 citizen petition (the Savient Petition) filed by Savient Pharmaceuticals, Inc. (Savient) are respectfully submitted under 21 C.F.R. § 10.30(d). The Savient Petition requests that the Food and Drug Administration (FDA) extend the scope of Savient's newly acquired three-year exclusivity for certain labeling changes to prohibit approval of any Abbreviated New Drug Applications (ANDAs) for generic oxandrolone products – even ANDAs submitted with labeling which excludes the protected language. As demonstrated below, there is no scientific or legal basis for FDA to take such action.

In fact, the Savient Petition is little more than Savient's transparent attempt to protect the market share of its biggest selling product. In its last annual report to investors Savient cautioned that the company's "financial results have been heavily dependent on Oxandrin sales," and that approval of generic oxandrolone products "would likely cause a

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significant decrease in our Oxandrin revenues, which would adversely affect us financially and could require us to scale back some of our business activities." Savient 2004 Annual Report at 3 (filed March 31, 2005). As with the company's earlier petition requesting that FDA impose unduly burdensome requirements on generic oxandrolone products[1], the Savient Petition was submitted in the hope that it will delay FDA's approval of generic oxandrolone while the agency researches and responds to the arguments raised therein, however frivolous. Oxandrin has been marketed for over 40 years. Even a single day's delay in approval of generic oxandrolone drug products is wholly unwarranted.

I. Factual Background

Oxandrin (oxandrolone) drug products have been marketed since the 1960s to promote weight gain after weight loss following extensive surgery, chronic infections, or severe trauma or in patients who fail to gain weight or maintain normal weight without definite pathophysiologic reasons. Savient purchased NDA 13-718 for Oxandrin in 1995. On June 2, 2005, Savient obtained approval of sNDA 13-718/S-023 which incorporates certain information regarding geriatric use of oxandrolone into the labeling of Oxandrin. The Summary Basis of Approval (SBA) for sNDA 13-718/S-023 has not yet been made publicly-available by FDA.

II. The Savient Petition is Based on a Fundamentally Flawed Legal and Scientific Rationale

A. Savient's three-year exclusivity is not a bar to FDA approval of an ANDA for an oxandrolone drug product with proposed labeling that omits the information protected by the exclusivity

The Waxman-Hatch amendments to the Federal Food, Drug, and Cosmetic Act (FDC Act) provide holders of New Drug Applications (NDAs) with three years of market exclusivity for changes approved in an NDA supplement where new clinical studies conducted or sponsored by that applicant are essential to the approval. FDC Act § 505(j)(5)(F)(iv). The exclusivity, however, applies only to the change, and not to the drug as a whole. Id. That is, three-year Waxman-Hatch exclusivity does not act as a bar to approval of ANDAs for non-protected conditions of use for which the reference listed drug (RLD) is approved. Specifically, the FDC Act, its implementing regulations and relevant

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[1] Docket No. 2004P-0074.

case law all recognize that information regarding exclusivity-protected changes to an approved drug can be carved out of proposed labeling submitted with an ANDA in order to permit approval of generic drugs for any remaining, unprotected conditions of use not rendered less safe or effective by the omission of such information. FDC Act §§ 505(j)(2)(A)(v), 505(j)(4)(G); 21 C.F.R. §§ 314.94(a)(8)(iv), 314.127(a)(7); *Bristol-Myers v. Shalala*, 91 F.3d 1493, 1500 (D.C. Cir. 1996).

Despite the well-settled nature of FDA's authority in this area, the Savient Petition appears to question, or at least lament, that authority.[2] As such, these comments will briefly review the basis for and judicial recognition of FDA's authority to approve generic drugs, the labeling of which excludes information on exclusivity-protected conditions of use of the RLD.

The FDC Act requires that an ANDA for a new drug contain, among other things,

> information to show that the labeling proposed for the new drug is the same as the labeling approved for the listed drug referred to in clause (i) except for changes required . . . because the new drug and the listed drug are produced or distributed by different manufacturers.

FDC Act § 505(j)(2)(A)(v). Similarly, FDA may refuse to approve an ANDA where information submitted in the ANDA "is insufficient to show that the labeling proposed for the drug is the same as the labeling approved for the listed drug referred to in the application except for changes required because . . . the drug and the listed drug are produced or distributed by different manufacturers." Id. § 505(j)(4)(G).

In implementing these provisions, FDA specifically noted that the

> [l]abeling . . . proposed for the [generic] drug product must be the same as the labeling approved for the reference listed drug, except

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2 "In many cases FDA has dramatically restricted the benefit of the exclusivity by approving generic drugs with labeling that contain all the labeling of the RLD's except that protected by the exclusivity." Savient Petition at 4. "FDA expanded on this section of the [FDC Act] in its implementing regulations, and specifically addresses changes from the label of the RLD that result from either patent protection or exclusivity granted under the [FDC Act]." Id at 10.

> for changes required because . . . the drug product and the reference listed drug are produced and distributed by different manufacturers. Such differences between the applicant's proposed labeling and the labeling approved for the reference listed drug may include . . . omission of an indication or other aspect of labeling protected by patent or accorded exclusivity under section 505(j)(4)(D) [now 505(j)(5)(D)] of the [FDC Act].

21 C.F.R. § 314.94(a)(8)(iv). Similarly, FDA will refuse to approve an ANDA if

> [i]nformation submitted in the abbreviated new drug application is insufficient to show that the labeling proposed for the drug is the same as the labeling approved for the listed drug referred to in the abbreviated new drug application except for changes required because . . . aspects of the listed drug's labeling are protected by patent, or by exclusivity, and such differences do not render the proposed drug product less safe or effective than the listed drug for all remaining, non-protected conditions of use.

Id. § 314.127(a)(7). FDA's implementation of the FDC Act through these regulations was upheld by the court in *Bristol-Myers v. Shalala*. There the court found that FDA had the requisite authority to approve ANDAs for the drug captopril where labeling for the ANDAs omitted an exclusivity-protected indication and dosing information specific to that indication. *Bristol-Myers*, 91 F.3d at 1500.

No contrary law exists on this point.[3] As such, and despite any implication to the contrary in the Savient Petition, FDA's authority to approve ANDAs for oxandrolone drug products which carve out labeling information regarding exclusivity-protected conditions of use is well-settled.

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[3] In fact, in both of the two citizen petition responses cited in the Savient Petition in ostensible support of Savient's position, FDA found that the ANDA applicant was permitted to carve out the labeling information in question.

B. Omission of labeling information regarding geriatric use in proposed labeling submitted with oxandrolone ANDAs would not render generic oxandrolone products less safe or effective than Oxandrin

The Savient Petition contends that approval of generic oxandrolone with labeling that omits geriatric use information recently added to the Oxandrin labeling would render the generic products less safe than Oxandrin because, in essence, they would omit information regarding a "lower and safer initial dose" in patients over 65 years of age. Savient Petition at 6. The new labeling language itself, however, suggests that generic oxandrolone products whose labeling carves out this information will be no less safe than Oxandrin. As discussed below, FDA has previously rejected similar innovator attempts to block generic competition by arguing that certain labeling language could not be carved out of proposed ANDA labeling because its absence would render the generic product less safe than the RLD. It should do so again here.

As recently required by the phased-in implementation of FDA's final rule on Addition of "Geriatric Use" Subsection in the labeling, sNDA 13-718/S-023 creates a "Geriatric Use" subsection in the PRECAUTIONS section of the Oxandrin labeling. 21 C.F.R. § 201.57; 62 Fed. Reg. 45,313 (Aug. 27, 1997). In discussing the effects of Oxandrin in patients over 65 years of age, the new labeling notes:

> Mean weight gain was similar in those ≥ 65 and those < 65 years of age. No significant differences in efficacy were detected between the 5 mg bid and 10 mg bid daily doses. The adverse event profiles were similar between the two age groups although the elderly, particularly in women, had a greater sensitivity to fluid retention and increases in hepatic transaminases.[4]

Failure to include this information in labeling for generic oxandrolone would not render those generics less safe. Notably, no new warnings or contraindications resulted from this

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[4] Savient Petition at 8-9; see also, Final Draft Labeling - submitted to FDA on May 20, 2005 for Oxandrin (oxandrolone tablets) C III *available at* http://www.fda.gov/cder/foi/label/2005/013718s023lbl.pdf (the Oxandrin labeling).

change.[5] In addition, information regarding fluid retention and increased transaminases remains unchanged in the ADVERSE REACTIONS section of the labeling.[6]

The new labeling also states: "Based on greater sensitivity to drug-induced fluid retention and transaminase elevations, a lower dose is recommended in the elderly (see DOSAGE AND ADMINISTRATION)." Savient Petition at 9; see also Oxandrin labeling. The dosing recommendation for geriatric patients (5 mg bid), however, falls within the dosing recommendation for adults generally (2.5 to 20 mg given in 2 to 4 divided doses). No new, lower dose has therefore been established. Thus the utility of the new language to prescribing physicians is more limited than suggested in the Savient Petition, and adequate information to label generic oxandrolone remains in the unprotected portion of the Oxandrin labeling.

The Savient Petition notes both that Oxandrin has been marketed since the 1960s and that the drug has been used, in large part, by geriatric patients. Yet the Savient Petition also claims that the newly added labeling information is "essential to the safe use of the drug in geriatrics patients." Savient Petition at 2. This seems implausible for changes that discuss already labeled adverse events and a recommended dose that falls within the already labeled doses for a drug with over 40 years of marketing history in geriatrics.[7]

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5 FDA has noted that "changes in labeling that involve warnings or other similar risk information" would not warrant exclusivity. 59 Fed. Reg. 50,338, 50,357 (Oct. 3, 1994). "Applicants obtaining approval for such changes in labeling would, in any event, have no valid interest in precluding such information from the labeling of other products." Id. By granting three-year exclusivity to information regarding geriatric use of Oxandrin FDA has already determined that the information is not essential risk information and is therefore not necessary to the safe use of the drug.

6 "ADVERSE REACTIONS . . . *Hepatic*: . . . Reversible changes in liver function tests also occur including increased bromsulfophthalein (BSP) retention, changes in alkaline phosphatase and increases in serum bilirubin, aspartate aminotransferase (AST, SGOT) and alanine aminotransferase (ALT, SGPT) . . . *Fluid and Electrolytes*: Edema, retention of serum electrolytes (sodium chloride, potassium, phosphate, calcium). Oxandrin labeling.

7 Placement of the new information in the Oxandrin labeling suggests that its clinical meaningfulness is unlikely to be significant. The geriatric use regulation requires

Moreover, information regarding increases in fluid retention or transaminases is contained in the unprotected portion of the labeling. In this situation, the omission of geriatric use information from generic oxandrolone drug labeling hardly renders any proposed generic drug product less safe than Oxandrin for all remaining, non-protected conditions of use such that ANDAs could not be approved under 21 C.F.R. § 314.127(a)(7).

Previous FDA determinations regarding the appropriateness of carving out subpopulation-specific dosing recommendations support this view. In its combined response to citizen petitions filed by Apotex Corp., Teva Pharmaceuticals USA and Caraco Pharmaceuticals Laboratories, Ltd, FDA determined that omission of a lower dose and titrated dosing information for patients intolerant of more rapid titration would not render generic tramadol drug products less safe than the RLD, Ultram.[8] FDA's response notes that there was a significant decrease in nausea and vomiting, clearly meaningful adverse events, on use of the protected titration scheme. As with geriatric patients taking oxandrolone, previously tramadol-intolerant patients taking tramadol represent a subset of patients in the unprotected portion of the labeling. Upon initial approval of generic tramadol products, their labeling was silent as to any special dosing or side effect profile in this subpopulation. FDA determined that such silence did not render generic tramadol less safe as contemplated in 21 C.F.R. § 314.127(a)(7) necessitating denial of ANDA applications omitting the carved-out language.

FDA similarly denied a petition on behalf of Valeant Pharmaceuticals International arguing, in part, that patent and exclusivity-protected dosing information on the use of ribavirin with PEG-Intron was essential to safe use of ribavirin since erroneous dosing could occur on the basis of generic labeling which included only a higher recommended dose of ribavirin for use with Intron-A.[9] There, FDA found that generic ribavirin whose

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NDA holders to review both their clinical trial information as well as spontaneous adverse event reports in proposing a geriatric use subsection. In the absence of an SBA for NDA 13-718/S-023, one can only assume that Savient complied with this requirement and that the lack of any geriatric-specific contraindications or warnings is indicative of a parallel lack of a significant safety signal in forty years of marketing without a geriatric use subsection.

8 See letter from Janet Woodcock, M.D., Director, CDER (01P-0495, 02P-0191, 02P-0252) (June 11, 2002).

9 See letter from Steven K. Galson, M.D., M.P.H., CDER (03P-0321) (April 6, 2004).

labeling omitted mention of PEG-Intron and lower ribavirin dosing of PEG-Intron patients was nonetheless no less safe than Rebetol for the remaining non-protected condition of use in combination with Intron-A. The situation presented in the Savient Petition raises even less of a safety concern than those faced by FDA in denying the citizen petitions related to tramadol and ribavarin.

C. Approval of oxandrolone ANDAs that omit the protected geriatric use labeling furthers the goals of the Waxman-Hatch amendments

The Savient Petition contends that the recently granted three-year period of exclusivity for geriatric information in the Oxandrin label provides it with "no market advantage" and suggests that this should be remedied by a grant of exclusivity for any and all uses of oxandrolone, thereby preventing generic competitors from entering the market for any indication. Savient Petition at 4. Such a reward, however, would far outweigh the research effort expended by Savient and would thwart the goal of the Waxman-Hatch amendments of bringing low cost generic drugs to market.

Despite the increasing awareness of and attention to issues involving use of prescription drugs by the elderly, it seems clear that neither Congress nor FDA intended to provide NDA applicants with an additional three years of exclusive marketing of a drug for carrying out geriatric research. The FDC Act is notable for its silence on geriatric research when compared, for instance, to the case of pediatric research. There, Congress clearly expressed its intent to reward NDA applicants with exclusivity for the overall drug product, not merely the new pediatric information if certain requirements were met. FDC Act § 505A. It is also notable that this reward of additional overall exclusivity is limited to six months. Any three-year Waxman-Hatch exclusivity granted as a result of pediatric clinical studies applies only to those new conditions of use that result from such studies and does not operate to block all generic competition for a period of three years. Lack of specific provisions in the FDC Act regarding exclusivity for geriatric research clearly indicates Congress' intent to limit three-year Waxman-Hatch exclusivity for geriatric studies to that condition of use alone.

Savient's complaint that the revised Oxandrin labeling is restrictive and would put Oxandrin at a competitive disadvantage to any generic oxandrolone product approved without such labeling appears to confuse generic oxandrolone drug products with other branded drugs approved for the same indication. That is, the Savient Petition appears to imply that generic oxandrolone manufacturers could use the disparity in labeling to market their generic products as somehow safer in the elderly – a situation which, of course, could not happen. It is difficult to believe that Oxandrin would lose market share to a generic

oxandrolone product merely because the Oxandrin labeling includes some clarifying language regarding geriatric use.

It is telling that Savient's press release announcing its submission of the subject citizen petition to FDA states that "[g]eneric Oxandrin would cut into market share of Savient's best-selling product, which generated 41 percent of Savient's net sales in 2004," and characterizes the petition as the second such petition filed by Savient, whose purpose is "to block generic versions of" Oxandrin.[10] Savient's concern then appears to be loss of sales to generic competition, however labeled, rather than geriatric safety or any disparity in "restrictiveness" between Oxandrin and generic oxandrolone labeling.

III. Conclusion

Approval of ANDAs for generic oxandrolone with labeling that omits geriatric use information recently added to the Oxandrin labeling falls squarely within FDA's authority and within the policy considerations underlying the Waxman-Hatch amendments. Such labeling would not render generic oxandrolone products less safe or effective than the listed drug for all remaining, non-protected conditions of use.

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[10] Savient Files Citizen Petition to Block Generic Oxandrin, Generic Line, Vol. 22, No. 19, at 3 (Oct. 5, 2005), *available at* http://www.fdanews.com/gl.

We appreciate the opportunity to submit these comments and look forward to FDA action on this issue.

Sincerely,

FOR

Robert A. Dormer

Josephine M. Torrente

RAD/JMT/tee/dh

cc: Sheldon Bradshaw
Elizabeth Dickinson